Amendments to the Specification:

Please replace paragraph **[0011]** with the following:

[0011] There is a need in the art for an improved method to deliver neuroactive agents from the systemic circulation across the blood-brain barrier and into the brain that reduces or eliminates some of the drawbacks and disadvantages associated with the prior art.

Please replace paragraph **[0015]** with the following amended paragraph:

In another embodiment of this invention, a composition is provided comprising a conjugate ~~of this invention~~ as described above and a pharmaceutically acceptable carrier. The composition can be directly administered into the ~~gneral~~ general circulation of an animal by any suitable means, e.g., parenteral injection, injection of intracerebral vein, and intranasal, pulmonary, ocular, and buccal administration.

Please insert after paragraph **[0018]**, and before the "Detailed Description of the Invention", the following:

Brief Description of the Figures

FIG. 1 is a plot showing the results of intracerebroventricular (i.c.v.) administration of an illustrative mPEG-2K-DPDPE conjugate (open triangles), morphine (open squares), and unmodified DPDPE (open circles) in male mice as described in Example 7. The results are plotted as percent maximum possible analgesic effect over time.

FIG. 2 is a plot showing the results of intravenous administration of an illustrative mPEG-2K-DPDPE conjugate (open triangles), morphine (open squares), and unmodified DPDPE (open circles) in male mice as described in Example 7. The results are plotted as percent maximum possible analgesic effect over time.

FIG. 3 is a plot showing the analgesic effect of five di-PEGylated biphalin conjugates of varying molecular weights compared to morphine and unmodified biphalin when administered intravenously in male mice as described in Example 7. The results are plotted as percent maximum possible analgesic effect over time.

FIG. 4 is a plot comparing the analgesic effect of an illustrative diPEGylated biphalin conjugate, an illustrative mono-PEGylated biphalin conjugate, morphine and unmodified

biphalin, when administered intravenously in male mice as described in Example 7. The results are plotted as percent maximum possible analgesic effect over time.

FIG. 5 is a plot comparing the analgesic effect of various doses of an exemplary diPEGylated biphalin conjugate when administered intravenously to male rats as described in Example 7. Results are plotted as percent maximum possible analgesic effect over time; and

FIG. 6 is a plot comparing the analgesic effect of an illustrative diPEGylated biphalin conjugate to unmodified biphalin when administered to male rats by both subcutaneous and intramuscular injection.

Please replace paragraph **[0061]** with the following amended paragraph:

[0061] Endomorphin II (H-Tyr-Pro-Phe-Phe-NH_2, 2.3mg) was dissolved in 1.15 ml of 5mM sodium phosphate buffer, pH 8.0. Modification of ~~Endomorphin~~ endomorphin II was performed in 1.5 hours at room temperature by adding $mPEG_{2000}$-SPA (38 mg) (mPEG succinimidyl propionate, MW 2,000) in a 5-fold molar ~~mole~~ excess. The reaction mixture was analyzed by mass spectrometry (MALDI) to determine the extent of modification. MALDI was used to verify that the reaction between $mPEG_{2000}$-SPA and ~~Endomorphin~~ endomorphin II went to completion. The sample was dialyzed against water using a 2000 MWCO membrane and lyophilized prior to *in vivo* assay.

Please replace paragraph **[0068]** with the following amended paragraph:

[0068] Doxorubicin hydrochloride (3.0mg, 5.2E-6 moles) was dissolved in 1.0ml of 50mM sodium phosphate, pH 7.2 buffer containing 150mM NaCl. The pH of the solution was titrated to 8.0 with 0.1N sodium hydroxide. A ten-fold molar excess of heterobifunctional PEG (NHS-PEG_{2K}-OPSS), NHS-PEG_{2K}-orthpyridyldisulfide was added to the doxorubicin solution. The reaction was allowed to proceed at room temperature for 2 hours. OPSS-PEG_{2K}-doxorubicin was purified from unreacted PEG and free doxorubicin using a Superdex 30 size exclusion column. The OPSS-PEG_{2K}-doxorubicin fractions were collected and lyophilized.

Please replace paragraph **[0074]** with the following amended paragraph:

[0074] ~~Dissolve~~ 118.7mg ~~mthoxy~~ of methoxy-PEG_{5K}-SPA (2.374×10^{-5} moles, 1.5 fold molar excess) was dissolved in 3.0mL anhydrous acetonitrile. Under a slow ~~Argon~~ argon flow,

~~add~~ 10.0mg ~~Biphalin~~ of biphalin (1.583× 10^{-5} moles of $-NH_2$ group) was added, followed by pipette addition of 4.4μL triethylamine (3.166×10^{-5} moles, 2.0 fold molar excess) into the solution. ~~Stir at ambient~~ The solution was stirred at ambient ~~for~~ overnight.

Please replace paragraph **[0075]** with the following amended paragraph:

[0075] ~~Evaporate~~ The solvent was evaporated via ~~on~~ rotary evaporator at 40°C ~~till~~ to near dryness, then further ~~dry on~~ dried under high vacuum for 5 minutes ~~(Use a liquid nitrogen trap when apply vacuum)~~. The residue was then dissolved ~~Dissolve the remaining~~ in 10mL deionized water. The solution pH ~~is~~ was 4.5. ~~Load the~~ The solution was loaded by injection into a prehydrated Slide-A-Lyzer dialysis cassette with 3500 MWCO (from PIERCE) and then dialyzed ~~dialysis~~ against 2×900mL deionized water over three days.

Please replace paragraph **[0076]** with the following amended paragraph:

[0076] ~~Load the~~ The solution was loaded onto a 2mL DEAE Sepharose column, and. ~~Collect~~ the eluent was collected. ~~Elute the~~ The column was eluted with an additional 125mL of deionized water, and ~~collect~~ the eluent (pH7.6) was collected. ~~Combine the~~ The two fractions were combined, ~~freeze~~ the solution was frozen in ~~by~~ liquid nitrogen, and then lyophilized ~~on a freeze dryer~~.

Please replace paragraph **[0077]** with the following amended paragraph:

[0077] ~~Dissolve~~ 141.4mg ~~methoxy~~ Methoxy-PEG_{12K}-SPA (1.187×10^{-5} moles, 1.5 fold molar excess) was dissolved in 2.0mL of anhydrous acetonitrile. Under a slow ~~Argon~~ argon flow, ~~add~~ 5.0mg of ~~Biphalin·2TFA~~ biphalin·2TFA (7.915×10^{-6} moles of $-NH_2$ group) was added, followed by pipette addition of 2.2μL of triethylamine (1.583×10^{-5} moles, 2.0 fold molar excess) into the solution. ~~Stir at ambient~~ The solution was stirred at ambient ~~for~~ overnight.

Please replace paragraph **[0078]** with the following amended paragraph:

[0078] The ~~Evaporate~~ solvent was evaporated under ~~on~~ high vacuum at room temperature ~~till~~ to dryness ~~(Use a liquid nitrogen trap when apply vacuum)~~. The residue was then dissolved ~~Dissolve the remaining~~ in 10mL deionized water. ~~Load the~~ The solution was

loaded by injection into a prehydrated Dialysis Cassette with 10000 MWCO (from PIERCE) and ~~dialysis~~ dialyzed against 2×800mL deionized water over three days.

Please replace paragraph **[0079]** with the following amended paragraph:

[0079] ~~Dilute the~~ The solution was diluted to a volume of 18mL by addition of deionized water. ~~Load the~~ The solution was loaded onto 10mL DEAE Sepharose column, and ~~. Collect~~ the eluent was collected. ~~Elute the~~ The column was eluted with an additional 90mL of deionized water. ~~Combine the~~ The fractions were then combined, frozen ~~by~~ in liquid nitrogen, and then lyophilized ~~on a freeze dryer~~.

Please replace paragraph **[0080]** with the following amended paragraph:

[0080] ~~Dissolve~~ 255.2mg Methoxy-PEG_{20K}-SPA (1.187×10^{-5} moles, 1.5 fold molar excess) was dissolved in 3.0mL anhydrous acetonitrile. Under a slow ~~Argon~~ argon flow, ~~add~~ 5.0mg ~~Biphalin 2TFA~~ biphalin·2TFA (7.915×10^{-6} moles of $-NH_2$ group) was added, followed by pipette addition of 2.2μL triethylamine (1.583×10^{-5} moles, 2.0 fold molar excess) into the solution. ~~Stir at ambient~~ The solution was stirred at ambient ~~for~~ overnight.

Please replace paragraph **[0081]** with the following amended paragraph:

[0081] ~~Evaporate~~ The solvent was evaporated under ~~on~~ high vacuum at room temperature until dryness ~~(Use a liquid nitrogen trap when apply vacuum)~~. ~~Dissolve the~~ The residue was dissolved ~~remaining~~ in 10mL deionized water. ~~Load the~~ The solution was loaded by injection into a prehydrated Dialysis Cassette with 10000 MWCO (from PIERCE) and ~~dialysis~~ dialyzed against 2×800mL deionized water over three days.

Please replace paragraph **[0082]** with the following amended paragraph:

[0082] ~~Dilute the The~~ solution was diluted to a volume of 25mL by addition of deionized water, and~~.~~ ~~Load the solution~~ loaded onto a 15mL DEAE Sepharose column. ~~Collect the~~ The eluent was collected, and ~~. Elute~~ the column eluted with an additional 150mL of deionized water. ~~Combine the~~ The fractions were combined, frozen ~~by~~ under liquid nitrogen, and then lyophilized ~~on a freeze dryer~~.